FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

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MEETING

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TUESDAY,

JULY 10, 2001

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The panel met at 8:00 a.m. in Salon A of the Gaithersburg Marriott Washingtonian Center, 9751 Washingtonian Boulevard, Gaithersburg, Maryland, Dr. Julie Swain, Acting Chairperson, presiding.

PRESENT:

JULIE SWAIN, M.D.	Acting Chairperson
SALIM AZIZ, M.D.	Voting Member
ROBERT M. DACEY	Consumer Representative
MICHAEL DOMANSKI	Consultant
MARK HAIGNEY, M.D.	Consultant
TED KAPTCHUK, O.M.D.	Consultant
WARREN K. LASKEY, M.D.	Voting Member
MICHAEL C. MORTON	Industry Representative
ILEANA PINA, M.D.	Consultant
JANET T. WITTES, Ph.D.	Voting Member
MEGAN MOYNAHAN	Executive Secretary

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

(8:02 a.m.)

DR. SWAIN: Would everyone please sign in. On the outside, there's some sign-up sheets. Welcome this morning. I'm Julie Swain. I'm a cardiovascular surgeon on the faculty at Harvard Medical School, but this year working at NASA on space station research.

And what I'd like to do first is to call this meeting to order, and it's a meeting of the Circulatory System Devices Panel, and this morning we're going to deal with the Guidant Contak CD and EasyTrak Lead System for the treatment of congestive heart failure.

There's a slight change in the printed agenda that you have for this afternoon, in that we'll have a break after the FDA presentation, which will be approximately 3:45 p.m.

First of all, I'd like to have our panel members and the people sitting at the table introduce themselves and their institution and their area of specialty.

MR. DILLARD: Jim Dillard. I'm the Director

of the Division of Cardiovascular and Respiratory Devices at the Food and Drug Administration.

DR. DOMANSKI: I'm Mike Domanski. I'm a cardiologist at the National Heart, Lung, and Blood Institute.

DR. LASKEY: Warren Laskey. I'm an interventional cardiologist at the University of Maryland.

DR. PINA: Ileana Pina, Heart Failure Transplantation, Case Western Reserve in Cleveland.

DR. HAIGNEY: Bart Haigney. I'm Director of Cardiology at Uniformed Services in Bethesda.

DR. KRUCOFF: Mitch Krucoff. I'm an interventional cardiologist at Duke Medical Center and the Director of Interventional Devices, Clinical Trials at the Duke Clinical Research Institute.

DR. WITTES: I'm Janet Wittes, a statistician at Statistics Collaborative in D.C.

MS. MOYNAHAN: I'm Megan Moynahan. I'm the Executive Secretary of the Circulatory System Devices Panel.

DR. AZIZ: I'm Salim Aziz, a cardiovascular

surgeon, University of Colorado, Denver.

DR. KAPTCHUK: Ted Kaptchuk, Assistant Professor of Medicine, Harvard Medical School.

MR. MORTON: I'm Michael Morton. I'm with W.L. Gore and Associates. I'm the industry representative.

MR. DACEY: I'm Robert Dacey, consumer representative from Boulder, Colorado.

DR. SWAIN: Thank you. Ms. Moynahan, read the conflict of interest.

MS. MOYNAHAN: The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants.

The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employer's financial interest.

The agency has determined, however, that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

We would like to note for the record that the agency took into consideration matters regarding Dr. Salim Aziz, Warren Laskey, Mitchell Krucoff, Mark Haigney and Ileana Pina.

Each of these panelists reported interests in firms at issue, but in matters that are concluded or not related to today's agenda. The agency has determined, therefore, that they may participate fully in all discussions.

The agency also would like to note that, due to the regulations governing covered relationships, the panel chair, Dr. Cynthia Tracey, will not participate in today's deliberations.

In the event that the discussion involves any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participant should excuse him or herself from such

involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. SWAIN: And just to remind you that anyone speaking in the public session or for the companies, before you speak, please introduce yourself, your name and position, whether you're an owner or own stock in a company, whether you're an employee of a company that's related to these devices, or whether you're paid for your transportation here or research grants, or things of that sort.

The first part of the meeting is an open public -- excuse me. One more. Voting status statement by Ms. Moynahan.

MS. MOYNAHAN: "Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, and as amended August 18, 1999, I appoint the following individuals as

voting members of the Circulatory System Devices Panel for this meeting on July 10, 2001: Mitchell Krucoff, Michael Domanski, Julie Swain, Ted Kaptchuk, Ileana Pina, and Mark Haigney. In addition, I appoint Dr. Julie Swain to serve as panel chair for the duration of this meeting.

For the record, Dr. Pina is a consultant to the Cardiovascular and Renal Drugs Advisory Committee of the Center for Drug Evaluation and Research, and the other individuals are consultants to this panel.

They are all special government employees and have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting." And it's signed by Dr. David W. Feigal, Director, Center for Devices and Radiological Health.

DR. SWAIN: Thank you. Now the first part of the meeting is an open public hearing and --

MS. MOYNAHAN: Sorry. I have one other thing. We'll have a few introductory remarks by Dr. Bernie Statland. Dr. Statland is the Director of FDA's Office of Device Evaluation.

DR. STATLAND: Good morning. My name is Bernie Statland. I'm the Director of the Office of Device Evaluation. My job is very easy. The people around me do all the work, and I have the opportunity of greeting you.

It's a very exciting day for all of us and, hopefully, by the end of the day we'll have learned a lot, we'll have gained a lot, and we'll move forward.

I would like to really extend three thank yous as we start off the day. I would first of all like to thank the panel members for coming here, giving up of your time, your expertise and your participation. Without all of you, we would not be able to move forward.

And, second, I would like to thank the individuals within the FDA, within the division headed by Jim Dillard, the Division of Cardiovascular and Respiratory Diseases, DCRD, for the tremendous amount of effort that they have placed.

But last but not least, I would like to thank the companies, industry, that really have invested their intellectual capital, their financial

capital and their initiative to bring forward devices that, hopefully, today and also other devices we'll hear about that will make a difference.

And without eating up any more of your valuable time, I welcome you. I hope it's a productive meeting, a meeting where there will be a lot of give and take. We'll learn something from it. And thank you all very much.

DR. SWAIN: Thank you. Okay. Finally, we'll get to the open public hearing part, and there were no prior requests to speak. Is there anyone in the audience who wishes to address the panel on this morning's topic?

If not, we will close the open public hearing part and we'll start with the sponsor's presentation and, again, remind you to introduce yourself, and your position, and any conflict. And this lasts approximately one hour.

MR. DeVRIES: Good morning. My name is Dale DeVries. I'm Vice President of Clinical and Regulatory Affairs for Guidant Corporation. I do own Guidant stock.

It's my pleasure to be addressing this panel and starting the discussion related to the first-ever PMA device that may be considered for approval, where we have cardiac resynchronization therapy in combination with an ICD.

I would also like to express my thanks for all the effort that went forward in bringing this to the panel today, in particular, to the FDA, the reviewers and all the staff at the FDA; to the panel members in preparation by review of the materials that were prepared and sent to you and considered for review today; to the clinicians and consultants who will be speaking on our behalf related to this trial; to my Guidant associates; to all the general public and other interested parties that are here today.

Why are we here today? Obviously, it's to review the existing evidence for the safety and effectiveness for cardiac resynchronization therapy when combined with an ICD that's already proven.

We'd like to confirm that there's a patient population that clearly benefits from this therapy and to make this important therapy available for the

management of heart failure patients.

I'll do a few brief introductory comments. Then we'll turn the presentation over to Pat Yong, a Principle Clinical Research Associate for Guidant. Pat will go through device description, methods and results of our trial.

He'll start the presentation by going over the safety and efficacy results for the all-patient population. Then he'll take a few moments to describe the process and rationale that we used in going through a subpatient population. Then Pat will review the safety and effectiveness of the second population.

In addition to that, we'll have a presentation by Dr. Higginbotham. He's an expert in exercise testing from Duke University. He will go through some of the tests that we used to evaluate functional status and quality of life and then make a few comments about the clinical evaluation and importance of these measurements.

Obviously, when you go through a new device and a new technology and you try to make it available to the general public, there are a lot of things that

may occur during the course of this journey.

One is, as we continue to learn, our basic knowledge level will grow. In addition to that, the evidence will continue to build related to the therapy and devices that we're considering.

Also, new tools might become available to physicians along the way. In addition to that, for corporations such as ours, technologies will improve. We'll incorporate the new evidence that we've gathered and include that in the new devices as we bring them forward, and this is occurring at an accelerated rate.

In addition to that, the clinical practices that physicians use in their health care of heart failure patients will change.

One of the things I wanted to do was just make a few comments about the activities that we had related to the study. First of all, we wanted to do an overview of the safety of this study.

Second, the effectiveness of the therapy, and in addition to that, we wanted to consider the benefit and risk associated with this device and this therapy, in particular, related to the Contak CD.

Safety. The device and the procedures are safe, and that is based on the information that we're bringing forward. In addition to that, we needed to make sure that we were not creating any additional harm for the patients who may receive this device.

Effectiveness. The trial did not achieve its primary endpoints for effectiveness. In fact, I wish I were standing in front of you here today with a nice package all tied up with a ribbon in a neat bow. It's not true.

The Contak -- the CRT trial that we brought forward did not achieve clinical significance. However, there is a significant amount of information collected in this trial related to the clinical benefit, where we have reasonable assurances of the benefit that will be received by the patients.

In addition to that, we want to spend some time discussing the rationale and identification of a product of a group of patients that clearly benefit from this therapy.

Cardiac resynchronization therapy is effective in patients with moderate to severe heart

failure; that is, clinically meaningful results.

Benefit versus risk. These patients are already indicated for an IC. This was one of the challenges that we have inside our corporation as we reviewed the results. It's important to remember that these patients are already exposed to the risk of getting an implantable device, in particular, an implantable defibrillator.

In addition to that, the benefits of CRT therapy outweigh the risk of placing a left side coronary venous lead.

I'd like to make a few comments about the overall process and study chronology for the study. I know some of you may have thought that the clinical section of the panel package that you received was fairly involved.

First of all, we started with the Ventak CHF study, the original design. That was a procedure that required opening of the chest to allow placement of the leads. The enrollment was fairly slow at the early phases of the trial.

We received feedback from physicians that

the incremental risk of placing the lead was greater than they wanted to have for some of the patients that were very, very sick. We had received this information early on when we were considering heart failure devices.

Our response to this was to develop an EasyTrak lead system for placement of the leads on the left side of the heart, without having such an invasive process.

In addition to that, we needed to modify the generator so that the connection system for the lead could be managed. This generator was the most recent version of the ICD that we had available on the market.

We continued enrollment and enrollment actually accelerated. We completed enrollment, which we refer to here as Phase 1. We enrolled approximately 250 patients.

On the very same day, ironically, that we completed enrollment in this first study, we received information from the FDA that the requirements for all sponsors of CRT trials had changed. They

wanted to make sure that we had a minimum of six months of continuous data on the control patient population. In addition to that, they wanted to have six months of continuous data for the arm of the study where we'd have the therapy included for the patients.

We managed to modify the trial, change the endpoints accordingly, and continue to enroll in the trial. Enrollment was completed at the end of 2000. The PMA was summarized based on a January cut-off and submitted to the FDA in February of 2001.

In addition to that which is customary for new devices and new therapies of this sort, we were asked to update the panel information related to the most recent cut-off related to this patient population so that you would have that information for consideration in your panel pack.

We're here today at the panel meeting. Now several other things occurred along the course of this trial. New drugs became available to physicians in the management of the heart failure population.

In addition to that, heart failure physicians and primary care physicians explained to us

one of their major goals was to keep heart failure patients out of the hospital. They have managed to do this. They have changed their patient management program for many of the population that have heart failure.

This study was no exception. There were multiple changes along the way. These changes were incorporated into trial and the resulting data that we have for you today.

So, in summary, there is a subgroup analysis that we have for you to consider. There's strong clinical evidence related to the performance of this device and this therapy.

The results are consistent with other trials, and the benefits are incremental to contemporary heart failure therapy treatment and also to patients who would also receive an ICD. There's a strong case for approval.

We did not do this trial alone. We had 47 centers involved in the trial and all of the support staff at those centers.

We have several physicians and consultants

with us here today. You can see that we have identified them by name, their clinical discipline, their study involvement, and their title affiliation.

As each one of these people speak, we'll ask them to disclose their affiliation, because they're very difficult to read.

First of all, Dr. Boehmer. Dr. Boehmer is a heart failure specialist and cardiologist. He's a member of our events committee and a principal investigator in this trial.

Dr. Foster is a cardiologist and director of our echo lab. Dr. Steve Higgins is an electrophysiologist and principal investigator in this trial. Dr. Higgins is also one of the largest enrollers and has a large body of information related to the use of this device and the lead system.

Dr. Larntz is an independent biostatistician. He was a statistical consultant for this trial, coaching and counseling us related to the activities as to how we summarized our information.

In addition to that, Dr. Larntz was also involved in some of the actual calculations and

statistical reports that we completed.

Dr. Mester is a cardiologist who has a lot of experience in vascular intervention. He's a principal investigator in this trial and has one of the highest success rates related to the lead implant and device use.

Dr. Mester was also instrumental in the development of some of the training programs related to this new therapy. We also have Dr. Saxon. Dr. Saxon is an electrophysiologist, a principal investigator in this trial, and a consultant in charge of our core lab.

We have several representatives from Guidant available for responding to your questions today. This is the group of individuals that will be responding to most of the questions you have today. It's obvious that the benefit of this product is very important and the clinical outcome is what most of judgement related to this product will be today. With that, I'd like to turn the presentation over to Pat Yong.

MR. YONG: Hello. My name is Patrick Yong

and I'm an employee of the sponsor. I'm going to start out with a therapy and device description, then move to the description of the stent design, and then finally to the endpoints and the associated results that support the indications we seek.

Patients who were enrolled in the Ventak CHF/ Contak CD study were all characterized as having dilated cardiomyopathy. Dilated cardiomyopathy is associated with ventricular remodeling and fibroid ingrowth as the heart enlarges.

As this fibrotic ingrowth invades the heart's natural conduction system, it may lead to a second important characteristic of this patient population, that of an intraventricular conduction delay, which is indicated by a white curex on the ECG.

This intraventricular conduction delay could lead to an asynchronous ventricular contraction with a loss of pumping effectiveness.

Cardiac rescynchronization therapy or CRT is intended to restore ventricular synchrony by pacing both ventricles simultaneously.

Unlike pharmacologic therapies that are

inotropic in nature, CRT has been shown to improve both ventricular function and increase the ventricular efficiency of the heart.

In order to achieve biventricular stimulation, we have to be able to pace the left side of the heart. And we do this by taking advantage of the coronary venous vasculature, which surrounds the surface of the heart. This gives us ready access to the left ventricle.

By placing a guide wire into the desired location in the coronary venous vasculature, a lead can be advanced, using the over-the-wire technique, similar to that used in interventional cardiology, to get the lead placed in its desired location.

On the left is the investigational EasyTrak lead. It's unipolar, has passive fixation, and has started moving. It rides over the guide wire to its final destination.

On the right is the family of guide catheters that are used by the electrophysiologist to help cannulate the ostium of the coronary sinus. It also serves as a conduit through which the lead is

placed into the heart.

The second mechanical component of the system is the Contak CD heart failure device. It's based on the commercially available Ventak AD3 ICD. and, therefore, has all the standard features associated with it: detecting arrhythmias, delivering shock for defibrillation and delivering anti-tachycardia pacing to treat monoformic V-tach. In addition to the EasyTrak lead, this device uses commercially available right atrial and left ventricular cardiodefibrillation leads. Because this device delivers both CRT and has ICD capability, we use the acronym CRTD to describe it.

In terms of how the device works, how we get biventricular sensing and biventricular stimulation, this diagram shows the header. In addition to the two normal ports that are used to connect the defibrillation leads and connect the right ventricular sensing and right atrial sensing leads, an additional port has been added to accommodate the EasyTrak lead.

This biventricular output is hardwired in the header itself, so the left ventricular output and

the right ventricular output are tied together. Therefore, we get both biventricular stimulation and biventricular sensing.

In this particular device, the outputs for the left ventricular and right ventricular channels are not independently programmable.

As a consequence of making the header this way, we optimize our biventricular and tachycardia pacing through ICD.

The device had to undergo a number of stringent tests before we could get to clinical trials, starting out with design verification testing, or DVT. For the Contak CD volt generator, or VG, it consisted of electrical and mechanical testing, testing of battery capacity, electromagnetic capability, as well as a software DVT for both the pulse generator and the program application which is used for programming the device.

There was also similar device verification testing that took place with the EasyTrak lead. The tests includes the axial load, electrical resistance, insulation integrity, pacing impedance, and fatigue

resistance.

We also tested the LV-1 connector, which was used in these track leads, and its compatibility with PG header. And finally, we had to consider how the lead worked with all the implant accessories that are used.

Once we considered the pace maker -- the PG load and the lethal load, we now have to consider them as a system. We had system design validation, including a systems feature test that simulated use under real-world conditions. We also had to look at safety risk analysis, including hazard analysis, reliability and friction analysis, and component qualification testing.

We also had to consider the biocompatability evaluation, the PG, the lead and the accessories. All this culminated in the animal studies, which were tested in a feline model.

Now we'll turn to the study design. The study was designed to demonstrate the safety and effectiveness of CRTD in the population study. The major criteria in the study included a VT/VF

indication for ICD implantation. Therefore, every patient enrolled in the study is going to undergo a device implant.

Furthermore, patients had to have symptomatic heart failure, which would be New York Heart Class II through IV, while on heart failure drug therapy.

Patients had to have left ventricular dysfunction and an interventricular conduction delay with a measured QRS of at least 120 milliseconds. Furthermore, patients had to be in sinus rhythm with no indication for a bradycardiac pacemaker.

In terms of the study's scope, this study was conducted at 47 investigational centers, with 581 patients enrolled.

Fourteen patients did not undergo an implant procedure. Sixty-six patients did undergo the implant procedure, but did not receive the investigational system, leaving the 501 patients implanted with the investigational system.

As Dale DeVries pointed out, this study was conducted in two phases. Phase 1 was the original

study design. When the study was originally designed, it was built to answer the question: Does CRT improve chronic functional status?

The original design was that of a randomized, double-blind, cross-over. We chose a cross-over design because our initial look was at patients who would be doing a thoracotomy, and we wanted to use the most efficient design possible to minimize the number of patients exposed.

To achieve double blinding, we had to turn to a team. We had one investigator, the electrophysiologist, who would be responsible for programming the device and he obviously would know if the patient was programmed.

But the second individual, who would be the heart failure specialist, would be responsible for following up the patient and that individual was blinded as to the pacing mode. Finally, the patient themselves are blinded as well.

The primary outcome is measured in terms of functional status. The patients were given an exercise test using a modified Naughton protocol on a

treadmill. This protocol was performed at the randomization visit, again in three months, and again at six months. Peak VO_2 would be used as the primary endpoint. The original sample size required for Phase 1 of 248 patients, were enrolled.

The diagram at the bottom shows how the study was laid out. What makes the Ventak CHF/Contak CD study unique in its design is the pressing need that patients had for an ICD.

All these patients have VT/VF, and it's important to get a defibrillator in them as soon as possible. So it wasn't always possible to insure that the patients were on the right medications or have adequate doses.

Therefore, what we did was to implant the device and give the physicians a one-month period of time. This one-month period of time would allow the patient to recover from the surgery, it allowed them to recover from any cardiac arrest or any arrhythmia they had.

But it also gives physicians the opportunity to adjust medications as need be before the randomized

study is carried out.

Patients were them randomized to get either three months of CRT, followed by three months or no CRT; or, alternately, three months of no CRT followed by CRT.

At the end of this intense study phase, patients were continued to be followed at three-month intervals for device evaluation and so forth to ensure the device is working properly long term.

After we enrolled our original sample size of 248 patients, there was a dialogue between Guidant and the FDA concerning the design of the study that was looking at CRT.

We then modified our study and went forward with Phase 2. By looking at Phase 2, we looked at six months of continuous data, rather than a cross- over design with a new primary hypothesis, that of determining: Does CRTD slow heart failure progression?

We still retained the elements of the original Phase 1, that we would still continue to look at whether or not CRTD improves chronic functional

status.

So the features of the new study design are as follows. Instead of a cross-over design with three months duration each, we have a parallel design with six months.

We also now consider morbidity and mortality as the primary outcome. Again, we retained the elements of the original design; that is, patients were implanted. We had no CRT for the first month to give physicians an opportunity to follow the patients and adjust the medications, and then the patients were randomized through the six months of CRT or six months of no CRT. Again, at the end of the six-month period, patients would continue to be followed.

In terms of how data were integrated between the two phases, the patients enrolled in Phase 1 would contribute data from the first three-month period. Patients enrolled in Phase 2 would contribute data throughout the entire six-month period.

Based upon the sample size available at the time of analysis, we have roughly half the patients in Phase 1, half the patients in Phase 2 for a follow-up

time four and a half months during the intensive therapy phase.

In terms of study organization, because it was important to consider the effect on functional status, we went through a core laboratory and they were used to evaluate all data from exercise testing.

We also used the services of a external events committee. It consisted of four electrocardiologists, with three heart failure specialists and one electrophysiologist serving.

It was their task to review and adjudicate all deaths and all hospitalizations that took place during the course of the study. Furthermore, this committee was blind to the randomized therapy while they made their deliberations.

We also had an independent statistician who provided statistical recommendations and helped perform the covariate analyses.

The patient demographics of the Ventak CHF/Contak CD study are very similar to that of a standard defibrillator population with a high proportion of coronary artery disease.

What's notable is that 58 percent of the patients are New York Heart Class III, and a left bundle branch block was the most predominant sort of interventricular conduction delay.

We also find that patients were very well medicated at the time they were treated in the study. We determined that there were no clinically significant differences between the CRT and the control groups at the time of enrollment.

Now we'll turn to the endpoints and the study results. We consider our results in three distinct ways. First of all, we have the EasyTrak lead. We'll look at it and its performance.

Then we'll look at what happens when we take the EasyTrak lead and combine it with CRTD to see how well it works as a system.

Finally, we'll consider CRT and how well it works as a therapy.

Starting with the EasyTrak lead, EasyTrak lead safety was determined on the rate of the lead-related adverse event rates. Effectiveness was judged in terms of lead performance, that is, pacing, sensing

and impedance. We also considered the implant success rate.

Shown on the left is the lead-related adverse event rate of approximately 12 percent. The 95 percent confidence -- 95 confidence interval is well within the acceptance boundary. Therefore, we do meet the safety endpoint.

Shown on the right are the three most common types of adverse effects associated with the EasyTrak lead. The first one is elevated left ventricular thresholds, which were seen in 29 patients, or 6.5 percent overall.

Twenty-five of these 29 were resolved with reprogramming -- I'm sorry. With repositioning, or 86 percent.

There were four patients in whom given the lead could not be repositioned or the investigator elected not to try it. That happened in 14 percent in which the therapy was abandoned.

The second most common type was that of double counting. Because of the biventricular sensing it's possible to sense the QRS twice, leading to

inappropriate therapy.

We saw that happen in ten patients, or in 2.2 percent. It resulted in lead reprogramming in five, resulted in lead revision in four, and one patient expired before lead revision could be carried out. However, that death was unrelated to the device or the therapy.

The third most common was that of coronary venous trauma, which was reported in ten patients, or 2.2 percent.

In all ten of these situations in the study, no intervention was necessary and no cardiac tamponade was noted. Furthermore, there was no short- or long-term sequelae resulting from these coronary venous traumas. Therefore, the adverse event rate is within our safety standards.

Turning now to effectiveness, what we first have to consider is getting the EasyTrak lead into the patient cannot be measured with the implant success rate.

Overall, we were able to implant the device in 87 percent of the patients in whom it was tested.

What we consider the number one reason for not being able to implant the device was either inability to locate the ostium of the coronary sinus or inability to cannulate it and get a stable position. That happened most commonly. When we take that into account, we were able to implant it in 91 percent.

We also considered the impact of a learning curve. Shown on the right is the patient population divided with quartiles based upon investigator experience. We find that over time with increased investigator experience, the implant's success rate rises over time. Furthermore, the ability to find and cannulate the coronary sinus os also improves as well. So investigator experience improving, we get to 91 percent in class success rate.

Also of importance is that of procedure time. The skin-to-skin time to place the entire system for the first quartile was about three-and-a-half hours. But as time goes on and investigators get more experienced, the mean time is now reduced to two hours by the time you get to the fourth quartile.

Let's now consider the effectiveness of the lead once it's in place. Starting out with left ventricular thresholds, the 95-percent tolerance interval was well within the boundaries set forth at the outset of the study.

Our threshold was about 1.8 to 1.9 volts throughout the study and was remarkably stable over time. The second effective set-point was that of lead impedance. This is the biventricular lead impedance and represents the parallel combination of the left ventricular and right ventricular leads.

The 95-percent confidence interval, again, is well above the standard set forth at the start of the study. Similar to the pacing thresholds, the lead impedance is, again, remarkably stable over time.

The third effective set-point was that the biventricular R-wave amplitude, or the ability to sense the rhythm. Very similar to the other endpoints, it was also stable over time with a mean value of about ten millivolts. The mean value was, again, well above the acceptance value.

So to consider the performance and safety of

the EasyTrak lead, all safety and effectiveness endpoints have been met.

Next we consider how the EasyTrak lead and CRTD, when used as a system, interact. In terms of safety for the implanted system, safety was measured in terms of the severe device-related adverse event rate and in terms of outcome mortality.

For effectiveness, we considered a combination of CRT and the EasyTrak lead to see how it affected ICD performance. The two regimens used here were detection time and a success rate of anti-tachycardia pacing or ATP for the termination of monomorphic V-tach.

Starting out with the safety endpoints, both the severe device-related adverse event rate and the outcome mortality rate were both well within the standards set forth at the outset of the study. Therefore, we meet the safety standard so we've combined the EasyTrak and CRTD together.

When we consider the performance of the combination, we started out looking at the induced ventricular fibrillation detection time. Because we

have two-lead sensing, we wanted to make sure that the combination of two-lead sensing did not do anything to degrade the ability of the device to detect induced VF and, clearly, we see that that doesn't happen.

The Contak CD average detection time was 2.2 seconds. That compares very favorably to that of a standard fibrillator, the Ventak AV1, of 2.0 seconds.

For ATP conversion efficacy, again, we have biventricular ATP. We first considered that of induced MVT, which is either tested at the time of implant, or it could be deferred.

This was tested experimentally in 44 patients. The conversion rate with CRTD was 64 percent. While this was less than we anticipated, it was similar to that of published studies about terminal testing of ATP by using the right side, which rated 59 to 80 percent.

We also tested the ability of the device to treat spontaneous MVT. In 196 patients, an empiric ATP scheme was used. The conversion rate of these episodes was 88 percent. Again, very similar to that of published studies for right ventricular ATP between 89

and 92 percent.

Therefore, ventricular fibrillation sensing and the treatment of ATP with biventricular ATP are similar to that for conventional ICDs.

To summarize the system's safety, for the EasyTrak lead, we demonstrated safety and effectiveness of the device. We also find that if we combine the EasyTrak lead as part of a system, that the system still remained safe and IC performance remains robust.

We also had additional experience as well in that there are two separate studies that can look at how well the EasyTrak lead system worked.

One is the continuation of the Ventak CHF/Contak CD study beyond the therapy phase. That's near completion. We also have the European Registry, which has been completed.

Both of these studies provided prospective longitudinal assessment of the Contak CD EasyTrak system and CD monitoring. The focus of these two studies are complementary.

From the Ventak CHF/Contak CD study, we

continue with our analysis on morbidity and mortality. From the European Registry, we get additional information about functional status.

Between the US and the European studies, we have over 1,500 patients enrolled. In the United States, we have over 500 patients enrolled at 47 centers. The mean follow-up time is 16 months.

We have over 100 patients now followed for over two years, with three and a half years being the maximum available to us now. The cumulative experience is over 7900 patient-months.

When you consider our European experience, we have enrolled 1,000 patients at 248 centers. The mean follow-up there is four months with a maximum follow-up of 20 months, with an additional 4400 patient-months of experience.

We'll now consider the third investigational component of the study, that of CRT effectiveness. We had complementary endpoints that were used to evaluate the effectiveness of CRT and they represent complementary perspectives.

Theses endpoints were prospectively powered

at 80 percent with a five percent alpha level. The first consideration is that of the progression of heart failure for our primary endpoint. This analysis considered events and the time it took to reach those events.

The three components consisted of all-cause mortality, hospitalization for heart failure, which lasted at least 23 hours and VT/VF events which required device intervention.

The complementary perspective without a secondary one, was looking at the functional status. The endpoints specified in the investigational plan were peak VO_2. This was measured with an assisted, limited exercise test performed on a treadmill and quality of life.

Quality of life was determined by the Minnesota Living with Heart Failure questionnaire. We also formed ancillary analyses that would help complement the functional status endpoints. We looked at six-minute walk, V_E/VCO_2 slope and changes in the New York Heart Class.

We also provided covariate analysis. The

purpose of the covariate analysis was defined as any factors other than treatment that could affect the outcome.

As stipulated in the protocol, clinically relevant variables were selected before processing any analysis for the primary and secondary endpoints at the conclusion of the study.

We utilized the services of physicians who formed our Contak CD events committee. They provided five variables, based on their clinical experience, that were associated by them with the progression of heart failure.

The five clinical variables provided were that of New York Heart Class, bundle branch morphology, etiology, whether ischemic or non-ischemic, left ventricular ejection fraction and the QRS width.

Once we have these covariants identified, we were then able to proceed with the primary and the secondary analyses.

In the primary analysis, we look at the time-to-event analysis and the progression of heart

failure and we were then able to look at the longitudinal analysis of functional status over time.

Starting with progression of heart failure, on the Y-axis is the result of reduction with CRT with respect to the control group with no CRT.

We find that a 56 percent relative reduction in mortality, 25 percent relative reduction in heart failure hospitalization and a 13 percent relative reduction in VT/VF events.

The composite endpoint was a 19 percent reduction overall, which was not statistically significant. However, every component of the index was consistent and in a direction favorable to CRT with no clinical evidence of harm.

When we considered the functional status endpoints, after six months of CRT in this patient population, we saw .7 milligram per kilogram per minute improvement in peak VO_2, which approached but did not achieve statistical significance.

With quality of life, we saw improvement in both groups, though we did not detect any statistically significant difference in quality of

life, between CRT and no CRT.

Turning now to the ancillary analysis, for a six-minute walk, we saw a 22-meter improvement in the CRT group after six months, compared to the control group. Similar to peak VO_2, it approached, but did not achieve statistical significance.

For the V_E/VCO_2 slope, again, after six months of CRT, we did not detect any differences.

The final ancillary analysis was that of New York Heart Class. After six months we see that 68 percent of the patients are New York Heart Class I or II, compared to 81 percent of patients after six months of CRT. Again, this approached but did not achieve statistical significance.

So to summarize our CRT effectiveness, statistical significance was not reached for the primary or the secondary endpoints. However, from the event analysis, we do see a positive directional effect of CRT upon all individual components of the index -- mortality, heart failure hospitalization and VT/VF events.

When we consider functional status, we also

see a modest trend toward clinical improvement with CRT in the indices of peak VO_2, six-minute walk and New York Heart Class.

So at the conclusion of the study, we sort of stepped back and reflected on what we had learned from the study and what we could determine.

First of all, let's consider what we've learned about the EasyTrak lead and the CRTD EasyTrak system.

We know the system is safe. The lead is safe; the combination of lead with the conventional ICD is also safe.

We also know the devices perform as designed, that the EasyTrak lead can be placed with high confidence in a decent amount of time, and electrical performance is stable as well. We also know that, when used as a system, that IC performance is not compromised.

In terms of CT, when you consider safety, we don't see any evidence that CRT is associated with clinical harm in this patient population. In terms of effectiveness of CRT, we see a positive directional

effect on the components of heart failure progression as well as trends to improvement in functional status.

We also see a high degree of physician and patient preference for the therapy. When we polled patients in the last follow-up conducted, 97 percent of the patients were programmed to CRTD at the last follow-up visit.

We also have to consider the results of the covariate analysis. The covariates provided by the Heart Failure Events Committee were able to identify for us a patient population with advanced heart failure. After looking at this patient population, that gives us encouragement to continue further looks.

The greatest improvements in peak VO_2 and quality of life were associated with the severity of baseline heart failure. That is, the more sick the patient was, the more likely you are to see improvement.

We also see emerging data from other studies as well. Published studies were conducted while the study was in progress, and the published evidence of CRT in a similar patient population also showed

results.

You can look at the French Pilot Study, which looked at Heart Class III/IV patients; the InSync Study, which looked at Heart Class III/IV; MUSTIC, which enrolled Class III; and PATH-CHF, which included patients with New York Heart Class III/IV heart failure. So positive results were reported in these other studies with a similar patient population.

This is what we know, but then we have to stop and consider what we don't know, and we have to walk through some questions. We first of all have to consider the risk/benefit ratio of CRT in the study populace with New York Heart Class III/IV heart failure.

First of all, we have to ask ourselves in terms of risk: Is it possible that CRTD in a specialized patient population could cause harm in a patient with advanced heart failure? We don't know if the lead or system safety looks different for these patients than for the general population. We also don't know the effect of heart failure progression in these patients as well.

On the flip side, consider benefit. Is it possible these patients may have a greater benefit in terms of heart failure progression and in terms of a functional status. We didn't know if it is possible that some or all functional status variables may show improvement.

And, finally, what is the magnitude of improvement, compared with other heart failure studies and that of other reported CRTD studies.

With that in mind, we decided to proceed with further analysis. We wanted to come to the impact of CRT on a subgroup of patients with advanced heart failure. We sought the Council for Independent Statisticians to advise the process, that first of all, multiple hypothesis testing must be kept to a minimum to avoid detecting any spurious results.

It was also decided to use the same five clinical variables obtained from the independent through -- excuse me -- an independent group of physicians and use those to do a separate analysis; and, finally, without any advance knowledge of what the impact of its covariates are, that the covariates

should be discrete. They should also be stable. We should consider covariates that are stable over time and are not in flux while the patient is in the study.

Baseline characteristics should be similar for the control versus CRT group and, importantly, p-values should be interpreted with care from this type of analysis.

Our observations should include a satisfactory sample size, and also importantly, that clinical merit is a reasonable consideration in assessing these findings. Therefore, with this plan and these ground rules in place, we then proceeded to further analysis.

Something else you have to take into consideration was to recognize that the New York Heart Class can change, that patients were enrolled in a class first, and then physicians had the opportunity to adjust medications. This was necessary because the VT/VF events were negative.

At the time of enrollment in the study, patients were predominantly New York Heart Class III. But before any intervention took place and while

physicians had the opportunity to follow their patients we see a shift towards higher heart classes. So a number of patients are now in New York Heart Class I or II who weren't there at time of enrollment.

It's the patients who remain in Class III or IV after the one-month waiting period that constitute the core of the advances heart failure group.

So let's consider the covariate analysis. Looking at our pre-specified endpoints of peak VO_2 and quality of life, we found that New York Heart Class III or IV patients had a statistically significant relationship with CRT.

We also saw that there was decreasing left ventricular ejection fraction and widening QRS. We also saw interactions with peak VO_2; however, not with quality of life.

When we consider etiology and bundle branch morphology, we found no relationships between these covariates and the outcome.

Therefore, it's the New York Heart Class III/IV patients at the time of randomization who were found to be the only covariate that had a

statistically significant relationship with both endpoints.

Furthermore, the subgroup of patients is consistent with that of other published studies, such as the French Pilot Study, InSync, MUSTIC. They all are considering a very similar patient population.

Let's look at the results we get from this analysis. Starting out with the sample size, roughly half the patients who enrolled in the study were advanced heart failure group and the sample size we obtained is similar to that we originally estimated for Phase 1 study, using parallel arms.

If we separate out these patients, and reconsider the endpoints for lead effectiveness, lead safety, system effectiveness and system safety, we find that we still meet all the safety and effectiveness endpoints for the subgroup.

So let's go back now and reconsider the question of heart failure. In this patient population, again, similar to that of the original all-patient population, we see that everything is moving in the right direction, it's consistent and

favorable towards CRT with respect to no CRT, and an overall 25 percent reduction in progression of heart failure. Again, no clinical evidence that CRT is harmful in this patient population.

We now walk through the functional status endpoints. The patients with advance heart failure after six months of CRT showed an impressive 2.1 mL per kilogram improvement over the control group, which pretty much stayed flat.

Quality of life in this patient population improved by nearly 11 points over the control group after six months of CRT.

For the six-minute walk distance, we found that a patient with CRT had a 48-meter improvement over those patients who were randomized to the control group. The V_E/VCO_2 slope was also favorable towards CRT with a 3.7-meter improvement.

We finally looked at the shift in New York Heart Class. We find that after six months of no CRT, 42 percent patients are now in the New York Heart Class I or II. After six months of CRT, 72 percent of patients are now near New York Heart Class I or II.

The results that we achieved are consistent with clinical expectations. We went to the literature to try to determine what represents a clinically meaningful change to V-tach. If we start with peak VO_2, that numbers between one and two mLs per kilogram per minute have been cited as the clinically relevant improvements for patient population, and we were able to achieve a 2.1 mL per kilogram per minute improvement.

The designers of the quality of life questionnaire designed it so that a five-point improvement would be clinically meaningful, and we were able to achieve an 11-point improvement.

In studies involving the six-minute walk test, it was true that you need to see an improvement of at least 45 meters to be clinically meaningful and in this patient population we saw a 14-meter improvement.

In studies with a V_E/VCO_2 slope, grades between minus three and minus 12 have been cited as clinically important improvements, and here we see a minus 3.7 unit improvement.

Based upon other published studies of heart failure, based upon other CRT studies that have been published, we are very consistent with what's already there.

So, finally, to summarize the relevance of the observed CRT effects in this patient population. First of all, the data we get are concordant. We have identified patients with advanced symptomatic heart failure who've been found to benefit with CRT. The data are also consistent.

First of all, when we look at all of the clinical variables, peak VO_2, quality of life, six-minute walk, V_E/VCO_2 slope or New York Heart Class, we see clinically meaningful changes in all of them, all of them in the direction that favors CRT.

Furthermore, if you look at our sample size, that's very close to the sample size needed to show the original functional status improvements in Phase 1 of the study.

It's also important to notice that the magnitude of changes we see are indeed clinically relevant. They match that of other heart failure

studies and are consistent with external studies which also consider CRT.

Finally, there's the effect of the meta-analysis. If we look at the individual components, we saw a positive directional effect of CRT upon all the individual components, again, with no clinical evidence of harm.

So, to summarize, for the Ventak CHF/Contak CD biventricular study, we believe we've provided reasonable assurance that the Contak CD EasyTrak system is safe and effective in the indicated patient population.

Let's first consider safety. That we either look at the lead or the system or CRT, it was found to be safe for the entire patient study and it was found to be safe in the advanced heart rate group.

This group is going to need to find its patients with New York Heart Class III/IV, while on heart failure drug therapy, left ventricular dysfunction, defined as a LVEF less than 35 percent, of a wide QRS, at least 120 milliseconds, and who are also indicated for an ICD. Physicians were to take in

all patients studied, as well as the advanced heart failure group.

We consider effectiveness. But the effectiveness of the devices themselves the EasyTrak lead and the system are effective for the entire patient population and remain effective in the advanced heart failure group.

Finally, in terms of CRT and its effectiveness, that we've demonstrated clinical assurance that CRT is effective in a patient population with advanced heart failure.

The clinical data before you supports the proposed labeling that we seek. With that I'll now turn the floor over to Dr. Michael Higgenbotham, who will comment on the clinical relevance.

DR. HIGGENBOTHAM: Thanks, Pat. Panel members, ladies and gentlemen. I must announce that I have operated as a core laboratory for cardio-pulmonary exercise testing in the Contak CD study and have no other interest in Guidant.

When you look at the functional status of heart failure patients, we sort of look at the

functional incapacity as leading to several different problems in patients with heart failure.

The primary problem, of course, is that these patients are unable to achieve certain levels of peak exercise and certain levels of sustainable exercise.

But there are some secondary problems that occur in a functional incapacity as well. They, of course, are the symptoms, the unpleasant symptoms of shortness of breath, and fatigue, and anxiety that accompany attempts to scope certain levels of physical activity.

And last but not least are the impacts that the functional incapacity has on interactions with other people, that lead to the very important financial and social impacts on the patient's quality of life.

So any worthy assessment of functional capacity in heart failure patients, of course, has to embrace those three sort of domains. The primary problem of functional incapacity and the consequences of it.

The Contak CD study achieved that. It achieved an appropriate selection of influence, which were these four measured here. The peak oxygen uptake, six-minute walk, quality of life questionnaire and the New York Heart Classification.

The peak oxygen uptake, of course, defined the level of peak activity this certain individual could obtain. The six-minute walk described another element of exercise, which is a sustained ability of exercise over a reasonable period of time.

And on the quality of life questionnaire that was used, assessed the patient's impression of the types of things that could be comfortably achieved in the physical domain in this questionnaire, and also the affect that that had on the patient's interaction with other individuals, the psychosocial consequences of functional incapacity and improvements in functional capacity.

Finally, NYHA class, which is the other important component of this sort of collage of this collection of functional evaluations looked at the patient's impression of how his incapacity affected

his day-to-day activities.

Now with those four, although they're all essential, peak oxygen uptake is somewhat the most robust. It's the most reliable measure of functional status because it's the only one of all of those measurements that objectively measures cardiac reserve.

Peak oxygen uptake is a pretty good non-invasive estimate, in fact, of exercise cardiac output. And I know we like oxygen uptake because it's independent of the protocol we used and of methods.

It doesn't matter whether there are minor departures from the protocol. It doesn't matter what instrument is used to measure exercise tolerance, and we get pretty much the same answer when we used maximal oxygen uptake.

And to those of us interested in exercise physiology, it also gives us a common language, a common currency with which to communicate.

An exercise time of five minutes means nothing to us. An exercise oxygen uptake of eight ml per kilograms per minute means everything to us.

Maximal oxygen uptake is important also because it's reproducible without a great amount of vulnerability to placebo or training effects.

This is -- it distinguishes maximal oxygen uptake from measurements like maximal workload, maximal exercise time, which are tremendously suspectable to differences in motivation, and differences in mechanical efficiency, which lead to progressive increase in exercise time, as we have well learned from a multitude of studies looking at pharmacologic interventions.

Finally, peak oxygen uptake is the endpoint that doesn't have to apologize to anybody. It is a primary measure of quality of life and an objective one that need not necessarily correlate with anything else.

It's very much the gold standard of the objective element of quality of life. One of the objections, of course, to maximum oxygen consumption is that day-to-day life is not a maximal event.

Surely, maximal exercise tolerance is not the determinative of a patient's ability -- a person's

ability to perform day-to-day activity.

That's true, except when you're a heart failure patient. It's true that in normal individuals a difference of 20 percent, even 50 percent of maximal oxygen uptake doesn't alter at all the extent to which you can carry out day-to-day activities.

But this illustration shows very well that the opposite prevails in patients who are impaired. If we take 20 cc's per kilogram per minute broadly as the low-end of normal, we see the impact and the relationship.

And this is a figure that I modified after Norman Jones' illustration. The greater the maximal oxygen uptake is reduced, the more impact it has on day-to-day activities.

In fact, it's not true that day-to-day life for an impaired heart failure patient doesn't get into the maximal oxygen uptake domain.

You can see that the sicker the patients are toward the left hand side of this curve, the steeper the relationship is.

And it makes sense that smaller increments

or decrements in physical capacity should have more profound influences on day-to-day activity the more people are impaired.

The second point made by this illustration is the two cc's of oxygen uptake is a lot. If you look at the difference between eight cc's per kilogram per minute, ten and 12, you're looking at completely different situations in terms of the independence of the patient's life.

And two cc's makes a difference between a patient that's stuck at home and one that can be taken out to see friends or to go to the mall with some assistance from friends or relatives.

Two cc's between the maximal oxygen uptake of ten and 12 gets them on the phone to their friends and relatives saying that they'll be going out by themselves. It's sort of the mark of independence when you get up to that maximal oxygen uptake.

They are the direct associations that shows you the magnitude that oxygen uptake has on the day-to-day quality of living.

Not only in the Contak CD study, where there

were these large changes, two cc's per kilogram per minute seen in the advanced heart failure group, but everything was concordant.

Not only as Pat showed you earlier, there were significant changes and concordant changes in the quality of life measurement, the six-minute walk measurement and this V_E/VCO_2 ratio. Increments seem to fall into place. Concordant moving in the right direction, but also according to the right quantity.

It's a little hard for you to think about a quality of life measurement of 10.9, but just consider for a moment what the physical equivalent of a 48 meter change is in a six-minute walk.

If you have a six-minute race between two heart failure patients and up to six minutes, one ends up 48 meters ahead of the next, you don't have to correlate that with very much to understand that that is a profound change in physical performance.

The V_E/VCO_2 ratio is a metabolical surrogate. It's a metabolic measurement that measures the excessive ventilation that occurs in heart failure patients out of proportion to the primary driver of

ventilation during exercise, namely, CO_2.

And what it describes is an increase in the dead space, a mismatch between ventilation and profusion of the lungs that happens because of the inadequate cardiac output that you're seeing in heart failure. So it measures the patient's ability to distribute blood to this particular organ.

And the problem with V_E/VCO_2, of course, is that it's a surrogate measure. The patient doesn't say I feel worse today because I my V_E/VCO_2 slope is a little bit higher. And that is a little bit of a problem in interpretation.

But there are two major advantages that make us keep on wanting to measure these measurements. Number one, they're mechanistic. That's so important for us in exercise physiology to know that the changes in exercise tolerance that we see have a mechanistic basis. It's something that you can't shake.

Now the second thing, talking of lack of shakeability, is the V_E/VCO_2 ratios. Very reproducible and it's not dependent on motivation. Most of the data that we see in this V_E/VCO_2 slope is from

submaximal domain of exercise, something you can't affect.

So it adds very much to the robustness of our confidence that in this subgroup of patients, something really was going on that was physiological.

Another thing I'd like to emphasize is that we hardly every see this kind of concordance or magnitude of exercise responses in pharmacologic studies.

I have personally not seen data over a six-month period where pharmacologic intervention safely improves exercise tolerance and gives such a beautiful concordance in all of the estimates of functional capacity.

It's not unique though because in other CRT studies, interestingly, show very similar data. I show here the three controlled trials that have been done with CRT and published fairly recently.

And without dwelling too much on statistical significance, because occasional -- in this grid have not achieved .05 statistical level of significance. But all of them have come very close. Most of

them have been significant and the qualitative and quantitative concordance in those three studies is remarkable.

When you think of the spotty or completely absent improvement in exercise tolerance in pharmacologic studies, three out of three isn't bad.

So I conclude that each of the endpoints selected for this study were good ones. They were totally appropriate. None of them was redundant. They weren't repetitive. They looked at different elements of functional incapacity.

They were complimentary, in that every one of them, not only reinforced the validity of the other in this subgroup, but added new information as to the clinical relevance of the findings.

And, of course, the important thing for us to consider is that CRT seemed to benefit this whole profile of objective and subjective measurements.

The changes that we were seeing in the functional status were positive, very internally consistent, implying that there is reality in these measurements.

The other thing that tends to reinforce my confidence in these objective and subjective measurements was that they compared very favorably with those observed in other heart failure studies, favorably in terms of pharmacologic studies, but very concordant with what was seen, what has been seen in other mechanical intervention studies.

We probably, more importantly, or as importantly to these findings being real, was that they were clinically important. The changes in magnitude of these meant that the types of clinical changes that you see, some metabolic measurements, some easier, like the six-minute walk test to interpret, had real clinical meaning for these heart failure patients.

So I conclude that this probably represents some sort of break through in this long struggle that we had to identify an intervention in heart failure. But over a very prolonged period of time, and it seems to get better as time goes on, we see a safe and effective improvement in functional class for these heart failure patients, and that, I think is a major

advance in heart failure therapy. Thanks a lot.

DR. SWAIN: Mr. DeVries. Does the sponsor have any further comments to make at this time? Great. Thank you very much and thank you for staying on time. Excellent presentations. The next will be the FDA presentation, Dr. Barold.

DR. BAROLD: Good morning. This PNA was submitted in what we call a modular form, meaning that the manufacturing information, the device description and pre-clinical and non-clinical laboratories studies were submitted prior to the clinical data, were avidly evaluated by the FDA and these modules have been subsequently closed.

Today we'll be presenting the information from the clinical module, which is the last module to be evaluated. Next slide, please.

The review team at the FDA was quite extensive, and I'd like to express my appreciation for all of the support that they helped to put this presentation together. Today you will be hearing from myself and also from Dr. Gerry Gray in regards to some of the statistical analysis. Next slide, please.

The preclinical testing was by the sponsor and I would just again add that the generator of these tests results have all been evaluated by the FDA and they met the appropriate standards for testing. Next slide, please.

Just as a basic device description to remind you, this is a full functional ICD and dual chamber pacemaker. It has a unique feature of biventricular pacing capabilities. This is achieved by tying both the right ventricular and left ventricular leads together and they receive both simultaneous sensing and pacing capabilities.

The EasyTrak left ventricular lead, which will also be evaluated today, was placed into the coronary vena system. Next slide, please.

The sponsor went through a complete study method, the phase one and phase two. Today he will be presenting the data from the phase two part of the study and just to remind you very briefly, that every patient received an implant.

These were patients that were indicated for an ICD, so every single patient got the same implant.

Then after a 30-day waiting period, the patients were then randomized to either the cardiac resynchronization therapy or pacing on or pacing off.

And then after the six-month point, the investigators were allowed to turn the cardiac resynchronization therapy on. And as you can see, the majority of the investigators did. Next slide, please.

I'd like to read you the indications for use of this device as defined by the sponsor. They are in patients who have advanced symptomatic heart failure, defined as New York Heart Association Class III and four, including left ventricular dysfunction in an ejection fraction less than or equal to 35 percent, a wide QRS complex defined as a QRS greater than or equal to 120 milliseconds while on heart failure drug therapy and patients who are at high risk of sudden cardiac death due to ventricular arrhythmias.

The primary study endpoint to this study were to show a slowing of the progression of heart failure as defined as a composite of all-cause death, heart failure related hospitalizations and ventricular

tachycardia and ventricular fibrillation requiring device therapy.

A modified endpoint, as was explained by the sponsor, also included adverse events for heart failure, and this would typically be patients that presented to the emergency room for diuretic therapy, but were not hospitalized.

The study was powered to detect a 25 percent reduction in the event rates, and I'd like to remind you that the control event rates were assumed to be a 15 percent death rate, a 30 percent rate for hospitalization for congestive heart failure and a 20 percent rate of ventricular tachycardia ventricular fibrillation.

These numbers were obtained from the Precise Study, which was a randomized placebo controlled study of carvedilol. Based on this, the sponsor calculated a sample size of 308 patients. Next slide, please.

Additional study endpoints included an improvement in the functional status, as measured by the peak VO_2, the V_E/VCO_2 slope and the six-minute hall walk.

They also measured the quality of life using the Minnesota Living with Heart Failure quality of life questionnaire, did a change in New York Heart Association function class, the ATP conversion efficacy, VT detection time, severe device related adverse events and operative mortality. Next slide, please.

They also looked at the appropriate study endpoints to evaluate lead efficacy and safety. Next slide, please.

The inclusion criteria the sponsor did talk about. I would just like to remind you that these are patients that are indicated for an ICD and, in addition, they had to have symptomatic heart failure, despite what was defined as optimal drug therapy, although not a specific New York Heart Association class was required to be included in this study.

The patients also had to have an ejection fraction less than 35 percent and a QRS duration greater than or equal to 120 milliseconds. Next slide, please.

The inclusion criteria are all listed here

and the major exclusion criteria were that they were not allowed to have a general indication for permanent pacing. Next slide, please.

The analysis performed, which our statistician will detail later, the primary endpoint used a rank-based method in survival analysis. The secondary endpoints using analysis of covariants. Next slide, please.

Patient accountability. There were 581 patients enrolled in this study. 501 were actually implanted and 490 randomized. There were 248 patients in the treatment group and 253 in the control.

In the advanced heart failure subgroup, which we will discuss later, there are 120 patients in the therapy group and 116 in the control group. Next slide, please.

These are the baseline characteristics of all the patients which the sponsor has detailed. I would just like to point out the New York Heart Association class at the time of implant, or at the time of enrollment, in which approximately one third of the patients were in Class II. There were no major

differences between the therapy on or off groups. Next slide, please.

At this point, I'd like to mention the change in New York Heart Association class from baseline, when the device was implanted, to 30 days later, when the patient was actually randomized in the study.

As you can see, there was a shift in the New York Heart Association class from the time of implant to randomization. This shift, however, was fairly equal between the two treatment groups.

And I would also like to point out that the advanced heart failure subgroup, which will be discussed later, consists of this group of patients here that are in Class III and IV at the time of randomization. Next slide, please.

These just outline the baseline characteristics of this advanced heart failure subgroup. They are very similar to the patient's characteristics associated with all patients, with the exception of the New York Heart Association class.

Now these are the baseline characteristics

at the time of implant. And as you can see, a certain percentage of those patients were in Class II heart failure and then advanced to Class III heart failure at the 30-day point. Next slide, please.

At this point, I'd like to turn the presentation over to our statistician, Dr. Gerry Gray.

DR. GRAY: Good morning. My name is Gerry Gray. I was the statistical reviewer for this submission. I just want to talk a little bit about some of the statistical issues regarding subgroup analyses and the AHF subgroup

There were, actually, two different subgroup analyses that have been submitted for this PMA. The first one, on the original round, was a subgroup called non-right bundle branch block, NYHA III/IV at enrollment. There are 290 patients in that group.

In the next round we have the subgroup that we're going to talk about now, the advanced heart failure subgroup, which consisted of patients who are NYHA class III/IV at randomization. And, again, that was one month after enrollment and implantation. There were 165 patients in common between those two

groups. Next slide.

There were five covariants that were defined or selected by the Heart Failure Events Committee for the analyses. NYHA class, bundle branch block morphology, ischemic or not, QRS width, left ventricular ejection fraction. And the NYHA class is the one that's being used to define the AHF subgroup here.

Again, I want you to recall that there was a one-month waiting -- a one-month transition period or waiting period between the time of implantation and the time of randomization. Next slide.

Now this graphic shows you, it traces out the NYHA class of all the patients in the study from the time of enrollment to the time of randomization one month later, and then at the six month follow up time.

And what this is -- there's a lot of stuff in here. But what you need to note mostly are these highlighted bars right there and right there that show you the amount of switching that went on between the enrollment time, when patients were implanted with a

device, and the randomization time, when the CRT therapy was turned on or not. Next slide, please.

The reason we look at that is because we want the covariants -- if you're doing a statistical analysis using covariants, you don't want them to be dependent on the treatment.

In other words, they should be something that was either measured before the treatment began or they are something that can't possibly be affected by the treatment, like age or gender.

And in this case we're talking about using NYHA class one month after implantation. And it certainly was before the CRT therapy was either turned on or not, but when you look at that graph previously, you wonder was that affected by the implantation.

Is the implantation in the following of the patients doing something to them that is actually -- might be part of treatment. I don't know.

A lot of that could just be due to something called regression to the mean. In other words, when patients were enrolled they were sicker and so one month later, they happen to -- a large portion or some

portion of them happen to get better.

And the problem here is that if the covariants are effected by treatment, then it's very difficult to interpret the results, because if you use a covariant that is affected by the treatment and adjust for it, then you're sort of adjusting for treatment to some -- it's very difficult to interpret what comes out in the end. Next slide, please.

Okay. Leaving all that aside for now, for the NYHA subgroup, if you're going to do -- use a subgroup analysis to make a judgement, there are a lot of caveats that you have to keep in mind when you're interpreting those results.

And I think the major one is that in general there's a tendency to over-interpret the significance of what you see.

And the main reason for that is because when you analyze multiple subgroups, when you look through and you use NYHA class or QRS width, or bundle branch block morphology, or whatever, to define a subgroup, the chance of finding one that is somehow, and this is in quotes, "significant" is very high.

And the P values -- statistically, the P values you get out from that are very difficult to interpret.

In this case we have five endpoints. Treating all the endpoints the same, we have five endpoints and we have five different covariants that you can use.

And you can use those combinations to create many, many different subgroups. So from a statistical point of view, you need to proceed with some caution here. Next slide, please.

Now from a statistical point of view now is there a justification for looking at this AHS subgroup by itself? And what I have here are five different criteria that you might use to judge a subgroup analysis.

First of all, is it prospectively defined? Was there enough information about that subgroup before the study even began that we knew in advance we were going to look at that subgroup? And the answer here is no.

NYHA class was defined as a covariant, but

it was not seen as any more important than any of the others, and it wasn't used to define any subgroup.

Secondly, is there a plausible biological explanation for the results that you see when you examine that subgroup. And in this case I think the answer is yes, based on the other information.

Is the subgroup analysis -- is it an analysis of the primary endpoint. Again, it was prospectively defined. In this case, I think no, based on the endpoints that we actually see that were significant.

Is there a treatment effect in the overall analysis? In other words, is there an effect of the treatment in the overall analysis that you see that something going on and you decide we're going to look and try to understand where this is happening, and the answer in this case is no.

And, finally, is there some interaction of the treatment with the variable that we've used to define the subgroup that would lead us to use that to focus in on that subgroup? And, again, the answer in this case is no.

Now there's another bullet that got left off of this slide, which is there some independent outside evidence that would lead you to this subgroup? And that's not mine -- I won't comment on that. Next slide, please.

So leaving aside now the question of whether or not we should have examined this subgroup or not, now that we are looking at the AHF subgroup, how are we going to judge the statistical significance of what we see?

And the question here is really what is a significant P value? And the problem is that statistically what you would consider a significant P value gets smaller with each subgroup considered and with each analysis that you do. It's really an adjustment for a multiplicity effect.

In this case, because we're looking at -- for the AHF subgroup, we're focusing in on the secondary endpoints, we really didn't define prospectively the analysis we were going to use. That wasn't agreed on in the IDE.

And in this case there are a bunch of

different analyses that you might have used that were all probably reasonable. You might be doing a single time point, versus some repeated measures, et cetera, et cetera. There's a long list of things that you might have done.

And probably even more important than that is a question of how many subgroups you considered before you arrived at the one that you're focusing in on.

In this case, I need to point out that exploratory analyses count. In other words, if you get your data and do -- make some graphs and do a few simple tests for a bunch of different covariants and based on that exclude some of them from consideration, you've really, in effect, tested those.

And whether or not you do a formal test at the end, doesn't really matter because you've looked at the data and used them to make that judgement. How much adjustment is necessary, because there's no way to really go back and understand how many subgroup analyses were even considered.

So just to summarize what I said, the use of

the NYHA class at the time of randomization one month after implementation raises some questions about its proper use as a covariant.

The justification from the statistical point of view, the justification for considering the AHA subgroup based on the data in this study is weak.

And finally, if you do go ahead and look at that subgroup, there really is a very difficult problem of how to interpret the P values that you get out to judge what is statistically significant or not.

So with that, I'm going to turn it back over to Helen to continue the presentation.

DR. SWAIN: Let's turn now to the actual data. This is the composite endpoint for all patients in this study. You can see it's broken down into death from any cause, hospitalization, the adverse events for heart failure and recurrent VTVF.

Now, again, the original endpoint did not include the adverse event for heart failure, but I will be talking about the modified composite endpoint.

You can see that there is a 23 percent reduction in the modified composite endpoint with a P

value of 0.12 and the exact numbers are listed here.

I just would like to remind you that the predicted control rates were quite different than what was actually observed. The observed rates were much lower than what was actually predicted. Next slide, please.

Here are -- it's just a graphical representation of that data that was put together by Dr. Gray for each of the four parts of the composite endpoint. Next slide, please.

And here's the composite endpoint for the advanced heart failure subgroup. You can see in this case that the event rates are a little bit closer in the control group to the predicted rates but, again, don't quite match that. There is a 29 percent overall reduction in -- seen in the advanced heart failure subgroup with a P value of 0.11. Next slide, please.

I'd like to examine the mortality that was seen in this study. In both groups there was 11 patients who died in the treatment group of all cause mortality, broken down into seven patients with a cardiac cause and four patients who died of pump

failure.

In the no pacing group, there was 16 patients who died of all cause mortality, four patients died of cardiac causes and nine patients died of pump failure. These are the P values for the two groups. Next slide, please.

From a functional standpoint, here's the data for the peak VO_2 and the all patient group for the three month and six month. And you can see the individual numbers listed here with the associated P - values. Next slide, please.

This is a graphical representation of this data, which shows the individual variability in this data and the control -- and the treatment group at baseline three months and six months. There are more patients, obviously, in the baseline to three months because those were the phase one patients.

And you can see the colored lines are the mean values for this. But you can see there's a tremendous amount of variability in the data. Next slide, please.

If you can, again, take out the advanced

heart failure subgroup and you compare from baseline to the six months, there was more of an improvement seen in the treatment group over the non-treatment group. Next slide, please.

As far as the V_E/VCO_2 slope, both groups showed an improvement in the all patient group. However, there was no significant difference between the groups. Next slide, please.

And here is the -- again, the individual data which, again, illustrates the high variability seen in all patients. Next slide, please.

Here's the data for the change in quality of life at three months and six months. You can see that both groups saw an improvement, both treatment and control, and you can see the incremental change at six months between the treatment and control with a P value of 0.44 Next slide, please.

Again, just to point out the incredible variability seen in the all patient groups here, and with the colored lines showing the means. Next slide, please.

Here is the advanced heart failure subgroup

data. And you can see -- well, there's a little bit of a problem with that P value there. You can see the data at three months and six months, and then incremental change seen between the two groups. Next slide, please.

And, again, here's the data for the six-minute hall walk at three and six months. You do see an improvement in both groups at the three and six-month points. The incremental change between the two groups and the associated P value. Next slide, please.

And, again, the data shows a tremendous amount of variability with the mean value shown in color. Next slide, please. And here is the advanced heart failure subgroup. You can see that the difference at six months between the two groups is 48 meters with an associated P value.

Next slide, please. This slide shows the change in New York Heart Association functional class in the all patient. These are patients that changed -- decreased by two or more, one, no change. And you see there isn't an improvement in both the treatment and the non-treatment group. Next slide, please.

And here's that associated change in the advance heart failure subgroup and you can see in the treatment group the numbers are quite low for this analysis, but there did appear to be more patients improved one or two classes in the treatment group. Next slide, please.

I'd also like to point out the ATP conversion efficacy. Remember that this device's primary effect is an implantable cardioverter defibrillator, so we need to assure that it is able to deliver that therapy.

They tested the conversion rate, or they looked at the conversion rate in the EP lab and the spontaneous conversion rate. I do think that the spontaneous conversion rate is what we should be looking at, and they showed an 88 percent success rate, and these numbers were similar in their advanced heart failure subgroup. Next slide, please.

Also very important to look at is the ventricular fibrillation detection time. And there was no significant increase in the detection time with the addition of the left ventricular lead and, again, the

data was for the advanced heart failure subgroup. Next slide.

Now, let's take a look at the severe device-related adverse events and operative mortality associated with this. The sponsor hypothesized this rate to be approximately 20 percent, and the actual rate was 1.2 percent.

During the study there were five generator failures, four of which required new implants. One was noted prior to implant.

The operative mortality was 3.4 percent for the thoracotomy procedure and 2.0 percent for the transthoracic procedure. In the peri-operative mortality there were 12 patients that died in the peri-operative period at a rate of 2.1 percent. Next slide, please.

This slide just illustrates the hospitalizations for heart failure in the all patients and the advanced heart failure subgroup.

You can see that there were 48 hospitalizations for congestive heart failure in the treatment group and 48 hospitalizations for heart

failure in the no treatment group.

And in the subgroup there were 36 hospitalizations for heart failure in the treatment group and 32 in the no treatment group. Next slide, please.

Let's take a look at the EasyTrak lead safety. There were 72 or 13.9 percent of patients had a lead-related adverse event, the most common of which was left ventricular lead dislodgement and there were 29 of those seen, or 6.5 percent.

Some of the more serious complications that we saw included five cases of coronary sinus perforations and one guide wire fracture that was subsequently removed by snare.

Sixty-nine patients could not have the Easy Lead Trak placed and the majority of those were due to problems located in cannulating the coronary sinus. Next slide, please.

One of the more important adverse events that we identified were incidents of coronary sinus trauma. Remember, that's what differentiates this lead implant from normal ICD's since you are putting

a lead in the coronary sinus. So it's important that we look at that particular part.

And we asked the sponsor to provide us data from all of their EasyTrak lead implants. They are using this in a number of studies, so we felt it was necessary to combine all of those leads.

So that's why you'll see in all of the EasyTrak lead implants and the information we have is 1,374 lead implants. There were 39 cases of coronary sinus trauma.

Out of those there were 20 dissections, 17 perforations, and two episodes of tamponade. 36 of these, or 92 percent resolved without any intervention.

Two of these caused subsequent death of the patients and there were possibly another two that may have been related to coronary sinus trauma. Next slide, please.

The sponsor did a very nice job of going through the EasyTrak lead results. But here's the exact data. The adverse events associated with the left ventricular lead was 10.9 percent and there was

a procedurally related adverse event of 13.9.

You can see that the implant success rate was 86.7 percent and the leads performed as the sponsor expected them to do. Next slide, please.

So as far as the EasyTrak lead points, the pacing thresholds stabilized after one month, which is to be expected with these leads, in that they're sensing an impedance endpoints. Next slide, please.

So in summary, the sponsor has met all the preclinical and manufacturing requirements for this device. They met their safety and lead performance endpoints. They did not satisfy the effectiveness endpoints when evaluating the all patients.

However, in the advance heart failure subgroup, there does appear to be more improvement with the cardiac resynchronization therapy in most of the functional implants.

At this point, would you like to discuss the PMA and then I'll read the questions, or would you like me to read them now?

DR. SWAIN: Actually, why don't you just quickly go over the questions to remind our panel

members that we need to have them address the questions.

MS. BAROLD: Okay. For the record then, I will go ahead and read the exact wording of the questions.

Question one, in the clinical report, section 4.3.1.4 identifies the adverse events, complications and observations for the system as a whole and each individual component, including the EasyTrak lead system.

Question 1A, the rate of coronary sinus trauma observed in this study with the EasyTrak lead was three to four percent. Please discuss safety issues associated with the implantation of a third lead in the coronary venous system and comment on whether the data in the PMA supports the safety of the lead system for the proposed indication.

Additionally, please discuss the clinical importance of the overall adverse events, complications, observations and comment on whether the data provides reasonable assurance of safety of this device system.

Question 2. The primary effectiveness endpoints in this study were composite of all cause mortality, hospitalizations for heart failure and episodes of ventricular tachycardia, ventricular fibrillation requiring therapy. The secondary endpoints for peak VO_2, V_E/VCO_2 slope, six-minute hall walk and quality of life questionnaire.

We ask you to please discuss the clinical relevance of the effectiveness endpoints for the patient population. The clinical study was designed with six months of follow up. Please comment on whether this point is adequate to provide a reasonable estimate of device safety and effectiveness.

A subgroup analysis performed on those patients with Class III and IV heart failure showed a more favorable outcome in the secondary endpoints. Please discuss whether the data in the PMA provides a reasonable assurance of safety and effectiveness in this group.

Question 3. The control group saw improvements in their functional status, quality of life, six-minute hall walk and New York Heart

Association functional class.

Please comment on this improvement in the control group as it relates to the improvement in the treatment group and if this relationship changes with the subgroup analysis of patients with advanced heart failure.

Additionally, please comment on the clinical relevance that this finding has on the observed effectiveness of cardia resynchronization therapy.

Question 4. Please discuss whether the data in the PMA provide reasonable assurance of effectiveness for this device in the patient population study?

Question 5. One aspect of the premarket evaluation of a new market is the review of its labelling. The labelling must indicate which patients are appropriate for the treatment, identify potential adverse events with the use of this device and explain how the product should be used to maximize benefits and minimize adverse events.

If you recommend approval of this PMA, please address the following questions regarding the

product labelling, as found in section three. In the indications portion of the labelling it states, "This device is indicated for patients with advanced symptomatic heart failure, as defined by New York Heart Association Class III and IV, including left ventricular dysfunction of wide QS complex while on heart failure drug therapy and have current indications for an ICD.

Based on the data provided, is this indication supported by the data provided? Please comment on whether the indication statement identifies the appropriate patient population for treatment with this device.

Also, please comment on the operator instructions as to whether they adequately describe how the device should be used to maximize the benefits and minimize adverse events. Please comment and provide any other recommendations or comments regarding the labelling of this device.

Question 6. Please identify and discuss the items that you believe should be contained in a physician's training program for this device. For

example, please comment on whether training should be required for proper placements of the EasyTrak lead system.

Question 7. Based on the clinical data provided in the panel packet, do you believe that additional clinical follow up or post-market studies are necessary to evaluate the long-term effects of biventricular pacing on heart failure.

If so, how would you design a study, including study design, duration, sample size, patient characteristics, for example, is a Q restoration of 120 milliseconds long enough to suggest significant ventricular desynchrony and what other measurements could be substituted, and what other additional potential endpoints should be looked at? That concludes the FDA presentation.

DR. SWAIN: Thank you very much. I have to comment that that was an excellent review by the FDA reviewers and the work that was put in. And the panel package is very well done. I still remember a decade or ago when we were given, I think, five to six feet of data, taller than me, to review. So I compliment

the FDA.

And what we're going to do is we're going to start having questions from our primary reviewer, Dr. Domanski, for approximately 15 minutes.

The way I run the panel is about 15 minutes from the primary, ten minutes from each of the other reviewers and then we just keep going in circles till everybody has all of the questions asked and answered that they wish.

So we'll start with Mike and then we'll take a break when Mike's finished for 15 minutes, and then reconvene. Mike.

DR. DOMANSKI: Well, I'm going to -- I do want to also compliment the FDA group that put this together. You know, you really did a beautiful job. It's very nicely done and I think it tells a story almost by itself that strikes me in looking at it as pretty straightforward.

I think I have some real concerns about this study, and I'm going to cut early to the chase on it. And what I would like to is I am very concerned that you have not demonstrated effectiveness of this device

with the studies you've presented.

But I don't want to be wrong about that, because a tremendous amount of effort and money and so forth goes into these activities, and it's important that one be smart about putting on the market things that are useful to the public.

But I do think that we -- I think that within this study you need to demonstrate effectiveness and safety, of course, and it has to be within this study.

We've had a -- this brief preamble is worth it to me anyway. I think that we've seen -- I've seen over many years now on this panel devices sometimes come to us that turned out to be quite useful as time went by, but which were not presented in a way that made that clear in the application.

And I'm concerned that that may be the case here. I'm not convinced that it's useful, but I think it may well be a useful maneuver.

So what I'd like to do is track through your effectiveness endpoints, using the FDA's workup and give you an opportunity to respond in a way that makes